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PHYSIOLOGICAL LABORATORY: HARVARD UNIVERSITY.

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Reprinted from the Boston Medical and Surgical Journal, May 21, 1874.

BOSTON:
PRINTED BY DAVID CLAPP & SON.
1874.

THE INFLUENCE OF ANÆSTHETICS ON THE VASO-MOTOR CENTRES.*

THE experiments reported in this paper were undertaken with the hope of contributing to our knowledge of the physiological action of anæsthetics by investigating the effect of these agents on certain nervous processes, which find their expression in changes of the arterial blood tension. The anæsthetic used in most of the experiments was sulphuric ether, but, for the sake of comparison, experiments with chloroform were also instituted.

As far as regards their power to produce insensibility to pain, anæsthetics may be regarded as antagonizing the effects of irritation of sensitive nerves. It is interesting, therefore, to inquire how far this antagonism extends to *other* effects of the same irritation. One of the most constant physiological results of irritation of a sensitive nerve is a rise of arterial blood tension, due to a reflex stimulation, through the vaso-motor centres of the muscular walls of the smaller arteries, especially those of the intestines. This phenomenon is so constant that its occurrence has been used as a test for the integrity of sensitive nerves, and a method of investigating the course of sensitive nerve fibres in the spinal cord has been founded upon it.†

Our first object was to determine the effect of anæsthesia on this reflex rise of blood tension. Since the contraction, reflex or voluntary, of the muscles of the trunk and limbs causes great irregularities in the blood tension, the phenomenon in question can be properly observed only when the possibility of such contraction is excluded. This can be most conveniently and effectually done by paralyzing the animal with curare, and keeping up life by artificial respiration. The experiments were, therefore, performed as follows. The animal (in most cases a dog) was confined upon the operating table in a supine position, and a dose of curare (varying, with the size of the animal, from two to ten cc. of a one-half per cent. solution) was injected into the external jugular vein. As soon as the respiratory movements ceased, the trachea was connected by means of a glass canula inserted into it with the apparatus for artificial respiration, which was so adjusted as to

* Read before the Boston Society of Medical Sciences, February 24, 1874.

† Miescher. Zur Frage der sensiblen Leitung im Rückenmark. Ludwig's Arbeiten. 1870. Page 172.

imitate as closely as possible the normal respiratory rhythm. A canula was then placed in the carotid artery and connected with a mercury manometer carrying a pen, by means of which the blood tension was recorded on a long strip of paper, which was kept in uniform motion by clockwork. (The rate at which the paper moved was recorded by means of a pendulum, which broke an electrical circuit once a second, and thus, through an electro-magnet, moved a pen which wrote upon the surface of the paper.)

The saphena nerve was then exposed and placed upon electrodes connected with the secondary coil of a Du Bois-Reymond induction apparatus, the primary current of which was supplied by one Grove cell. The irritation of the nerve was produced by closing the primary circuit by means of a key provided with a pen, which also wrote upon the paper directly under the pen recording the blood tension. The duration and the effect of the irritation could therefore be seen at a glance.

After determining the effect on the blood-tension of irritation of the saphena nerve, which was invariably a rise, amounting, usually, to from thirty to sixty mm. of mercury, the tube of the respiration apparatus was connected with a bottle containing ether, in such a way that the air was forced into the lungs of the animal, mixed with the vapor of the anæsthetic. After the ether had been administered in this way for several minutes, the saphena nerve was again irritated, and the effect noted. The ether was then removed, the animal allowed to breathe pure air, and the nerve once more irritated in order to determine, by comparison with the effect of the first irritation, whether the nerve still retained its irritability. Between the periods of irritation, the nerve was removed from the electrodes and restored to its position amongst the tissues of the limb. One great obstacle to the successful performance of this experiment was the impossibility of determining when a sufficient amount of ether had been given to produce anæsthesia, and when the effects of ether had been removed by breathing pure air; for the relaxation of the muscles, the usual sign of complete anæsthesia, had already been produced by the curare. The want of constancy in the results, to be attributed, in part perhaps, to this difficulty, renders it undesirable to give minute details of the experiments. Suffice it to say that in the majority of cases the rise of blood tension consequent upon the irritation of the saphena nerve was less marked when the animal was under the influence of ether than when the anæsthetic was not used. Frequently, no great difference could be observed, and in one or two instances, especially at the beginning of the ether inhalation, the irritation of the nerve caused a more decided rise of tension than without the ether. Subsequent irritations, however, had generally a diminished effect, showing that, in this respect, the influence of ether developes itself slowly, and is, perhaps, preceded by a period of stimulation. These effects are shown by the curves represented in figures 1 to 11 inclusive.* These curves are traced directly from the records of the manometer, and, in studying them, it must be borne in mind that, owing to the mercury descending in one leg of the manometer as it rises in the other, the recorded variations of blood-tension are only one-half the absolute variations. The curves are drawn from right to left, and the horizontal lines under

* See explanation of figures at end of article.

them indicate the time during which the irritation was applied to the nerve. The numbers over the horizontal lines indicate the intensity of the irritation in arbitrary units of the Du Bois-Reymond induction apparatus,* one Grove cell supplying the electrical current. The vertical column of figures on the right of each curve is a scale giving the absolute blood-tension in millimetres of mercury.

Far more constant were the results obtained by the use of chloroform. Our experiments with this agent were not so numerous as those with ether, but the uniformity was sufficiently great to justify a conclusion as to its action. It was invariably found that, when an animal was under the influence of chloroform, irritation of the saphena nerve caused a much less marked rise of blood-tension than when the anæsthetic was not used. Sometimes there was absolutely no rise of tension to be observed, while at other times the rise was from one-third to one-half that produced by the same irritation on an animal not subjected to the action of chloroform. This effect is shown by the figures 12 to 15 inclusive, which represent the results of irritations of the saphena nerve made alternately with and without chloroform.

Now when the intensity of any reflex phenomenon is affected by the action of a drug, or any other external agency, this *may* take place in three different ways, viz.: through a change of irritability, either of the afferent or of the efferent nerves involved, or of the nervous centres through which the action takes place. It is, therefore, of interest to inquire in which of these three different possible ways chloroform diminishes the reflex contraction of the bloodvessels consequent upon the irritation of sensitive nerves. This can only be determined by experiments in which one or the other of these three possibilities can be excluded.

Now it was shown by Nawalichin† that compression of the two carotid arteries causes a great increase of blood-tension, due to an irritation of the vaso-motor centres, produced by the diminished supply of blood sent to them. Our next object was, therefore, to determine how a rise of blood-tension produced in this way is affected by chloroform inhalation. For this purpose, a dog was curarized, and kept alive by artificial respiration. The mercury manometer was connected with the crural artery, and the blood-tension recorded in the manner above described. The two carotid arteries were then exposed, and a thread placed loosely around each. At a given signal, the two threads were raised simultaneously, stopping the flow of blood through the arteries, and causing a very decided rise of blood-tension. Chloroform was then given, as in the former experiments, and the arteries again compressed. Little or no rise of blood-tension was now observed. This result is shown in figures 16 and 17, where the effects of compression of the carotids, both with and without chloroform, are given. Unfortunately, only one experiment of this sort was performed, but the result was so marked that we may fairly conclude that the rise of blood-tension due to anæmia of the vaso-motor centres may be prevented by the inhalation of chloroform. Here the effect of the anæsthetic must be to produce a diminished irritability, either of the vaso-motor centres or of the vaso-motor nerves, the third possibility above mentioned, viz., the diminished irritability of the sensitive nerves being, of course, excluded. It is, therefore, a reasonable inference,

* The maximum intensity, i.e., with coils pushed together, being indicated by 1000.
† Centralblatt für medicinische Wissenschaften. 1870. Page 483.

in those cases where chloroform was found to diminish the reflex contraction of the bloodvessels, that this effect was due not to any influence upon the sensitive nerves, but to a diminished irritability either of the vaso-motor centres or of the vaso-motor nerves. Which of these two possibilities is the more probable is a question on which the observations of Scheinesson* throw light. This observer found that, when an animal was under the influence of chloroform, no unusually strong irritation of the cervical sympathetic was necessary in order to cause a contraction of the vessels of the ear. In other words, the vaso-motor nerves had, under chloroform, preserved completely their normal functions. If, therefore, chloroform does not diminish the irritability of the vaso-motor nerves, then the effect of this anæsthetic in checking the rise of blood-tension consequent upon compression of the carotids or irritation of sensitive nerves, must be due to a diminished irritability of the vaso-motor centres.

Another very frequent, though not absolutely constant result of irritation of sensitive nerves, is a diminished frequency of the heart-beats. This diminution begins usually soon after the blood-tension has reached its maximum, and continues often 20″ or 30″ after the irritation has ceased and the blood-tension has returned to its normal level. A slight and temporary acceleration of the heart-beats, coincident with the rise of blood-tension, not infrequently precedes this retardation. That this phenomenon is due to the influence of the vagus nerves on the heart is evident from the fact that after the section of these nerves no such result is produced. This is proved by the tracings represented in figures 18 and 19, showing the effects on the blood-tension and on the rate of the heart-beats of two irritations of the saphena nerve of equal intensity, applied one before and the other after section of the vagus nerves. It will be seen that after the section, though the blood-tension rises in consequence of the irritation of the sensitive nerves, the retardation of the heart-beats is absent. This retardation must, therefore, be due to an influence proceeding from the vagus centres along the vagus nerves to the heart. Whether this stimulation of the vagus centres is a direct effect of the irritation of sensitive nerves, or an indirect effect, consequent upon the rise of blood-tension, need not at present concern us. Our next object was to determine the effect of anæsthetics on this reflex irritation of the vagus nerve. The experiments performed for this purpose were the same as those for determining the effect of anæsthetics on the reflex rise of blood-tension, for the quicksilver manometer records the heart-beats, as well as the blood-tension. It must be borne in mind, however, that the reflex rise of blood-tension is a far more constant phenomenon than the reflex retardation of the heart-beats, so that only a small proportion of the experiments made were available for the study of the latter question. The results of these experiments were not perfectly constant, but in the large majority of cases it was found that the inhalation of ether prevented the reflex retardation of the heart-beats from manifesting itself. In several cases, the irritation of the sensitive nerve caused a decided acceleration of the heart, the temporary and slight acceleration above alluded to as often occurring without ether, becoming under ether a more marked and prolonged effect. This is to be seen in Figs. 20 to 22 in-

* Centralblatt für medicinische Wissenschaften. 1869. Page 506.

clusive, showing the effect of irritation of the saphena nerve before, during and after ether inhalation.

The experiments with chloroform were not conclusive, inasmuch as the phenomenon in question did not manifest itself distinctly in the cases where this anæsthetic was employed.

Our experiments enabled us to study the direct effect of chloroform and ether on the normal blood-tension and pulse rate, though this was not the object with which they were undertaken. In regard to the effect on the blood-tension, a great difference was noticed in the two anæsthetics. While the inhalation of chloroform caused, invariably, a decided depression of the blood-tension, varying in the different observations from 8 to 37 mm. of mercury; ether, on the contrary, caused, in the majority of instances, a marked rise of tension, varying from 9 to 51 mm. of mercury, and in those cases where the tension seemed to be lowered by ether, this depression was never greater than 6 mm. of mercury. This same difference between the two anæsthetics was observed by the committee appointed by the Royal Medical and Chirurgical Society to inquire into the uses and the physiological, therapeutical and toxical effects of chloroform.* The conclusion of the committee, however, that the diminished blood-tension under chloroform is due to an enfeebled action of the heart, cannot be accepted as expressing the whole truth, for a lowered blood-tension may also be caused by a diminished activity of the vaso-motor centres, and the experiments of Scheinesson above referred to render it probable that chloroform acts in both of these ways.

No positive conclusions as to the effect of anæsthetics on the pulse rate can be drawn from our experiments. Chloroform caused, in some cases, an acceleration, in others a retardation of the pulse. The effect of ether was likewise variable. The recorded observations of Scheinesson and of the committee of the Medical and Chirurgical Society are also at variance with each other on this point. The question can only be settled by new investigations directed particularly to this subject.

In experiments like those above described, where the effects of successive nervous irritations are to be compared, it is, of course, of the greatest importance that the method of stimulation should be such as to secure the greatest possible uniformity. The Grove's element, and the sliding induction coil of Du Bois-Reymond, leave nothing to be desired as far as constancy and convenience in the production of electricity are concerned; but, in the application of the electrodes to the nerve, certain difficulties are met with. If the nerve is allowed to lie upon the electrodes during the interval, often several minutes in duration, between two successive irritations, there is great danger of its losing its irritability by drying and stretching. On the other hand, if the nerve is removed from the electrodes and restored to its normal position among the tissues, it is impossible to replace it upon the electrodes with perfect certainty that it rests upon them in precisely the same way as during the previous irritation. Of these two sources of error, the latter is probably the lesser, and the nerve was accordingly in our experiments always restored to its place among the tissues between each two irritations. In view, however, of the difficulties inherent in this method of experimenting, it would be unwise to regard as conclusive any results except those of the most positive kind.

* Medico-Chirurgical Transactions, vol. 47, p. 323. London. 1864.

We must, therefore, content ourselves with presenting the following conclusions, as possessing, at most, only a high degree of probability:

I. Chloroform inhalation lowers the reflex irritability of the vaso-motor centres, thus diminishing the power of an irritation of sensitive nerves to cause a rise of blood-tension.

II. Ether acts, if it acts at all, much less powerfully, in this respect, than chloroform.

In other words, while ether and chloroform resemble each other in their effect on those nervous centres whose activity is connected with the conscious perception of pain, the latter acts much more strongly than the former upon those centres which regulate the arterial blood-tension, and thus affects profoundly the conditions of animal life. Ether and chloroform are, therefore, both anæsthetics, but chloroform is, also, something more.

To complete this study of the comparative action of ether and chloroform, many other experiments are needed, both to confirm the results already reached, and to settle new questions arising in the course of the investigation. The subject would not be presented in its present imperfect form, were it not that the departure of one of us for Europe has made it necessary to interrupt, for the present, the series of experiments.

EXPLANATION OF FIGURES.

Figs. 1 to 11 inclusive show the effect of ether inhalation on the rise of blood-tension, caused by irritation of sensitive nerves.

Fig. 1, before ether inhalation.
Fig. 2, after 2′15″ ether inhalation.
Fig. 3, after 4′20″ ether inhalation.
Fig. 4, 4′40″ after removal of ether.
Fig. 5, after 5′ ether inhalation.
Fig. 6, after 8′ ether inhalation.
Fig. 7, 6′ after removal of ether.
Fig. 8, before ether inhalation.
Fig. 9, after 4′40″ ether inhalation.
Fig. 10, after 10′30″ ether inhalation.
Fig. 11, 5′40″ after removal of ether.

Figs. 12 to 15 inclusive show the effect of chloroform inhalation on the rise of blood-tension, caused by irritation of sensitive nerves.

Fig. 12, before chloroform inhalation.
Fig. 13, after 3′ chloroform inhalation.
Fig. 14, 3′45″ after removal of chloroform.
Fig. 15, after 3′30″ chloroform inhalation.

Figs. 16 and 17 show the effect of chloroform on the rise of blood-tension caused by compression of the carotid arteries.

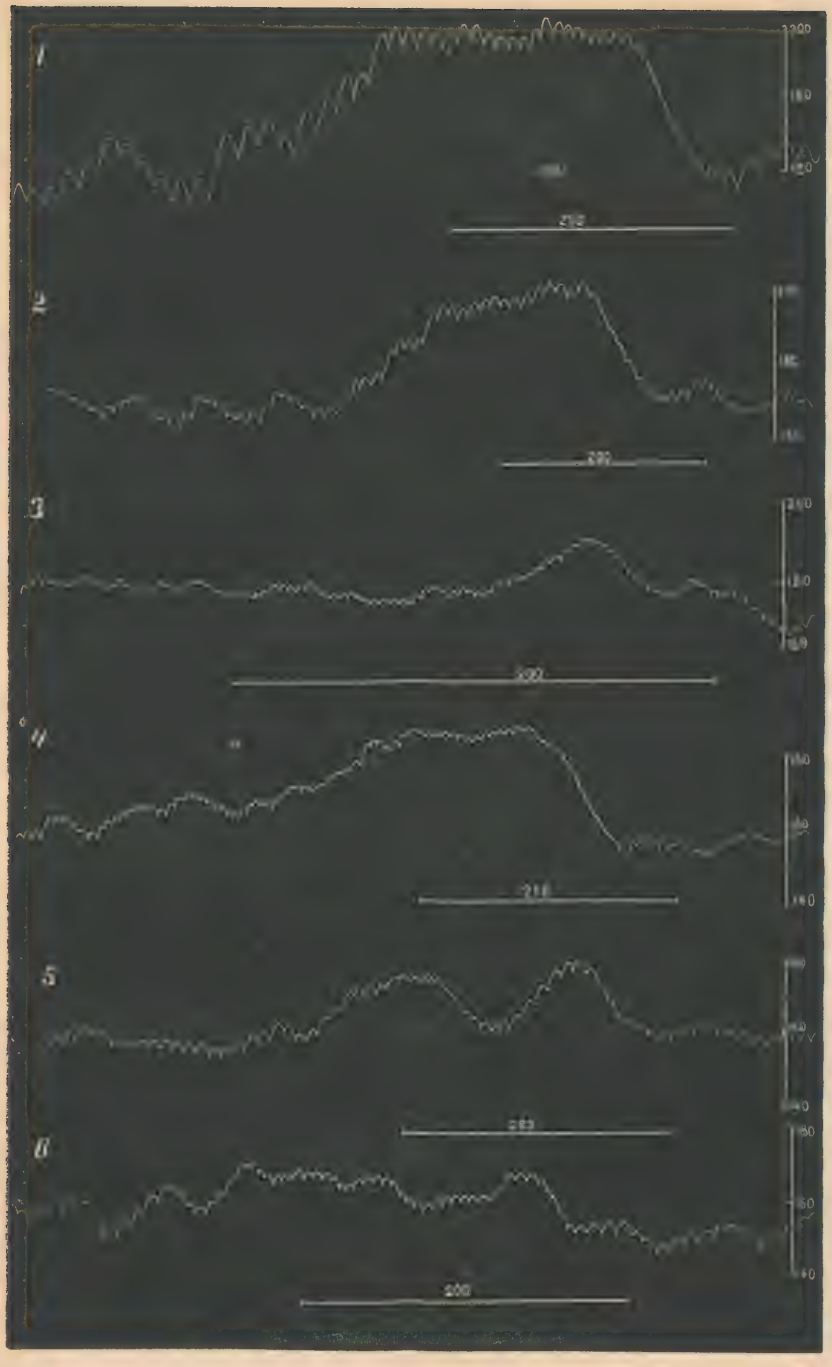
Fig. 16, without chloroform.
Fig. 17, during chloroform inhalation.

Figs. 18 and 19 show the effect of section of the vagus nerves on the changes of pulse-rate caused by irritation of sensitive nerves.

Fig. 18, before section of vagus nerves.
Fig. 19, after section of vagus nerves.

Figs. 20 to 22 inclusive show the effect of ether inhalation on the changes of pulse-rate caused by irritation of sensitive nerves.

Fig. 20, before ether inhalation.
Fig. 21, during ether inhalation.
Fig. 22, after ether inhalation.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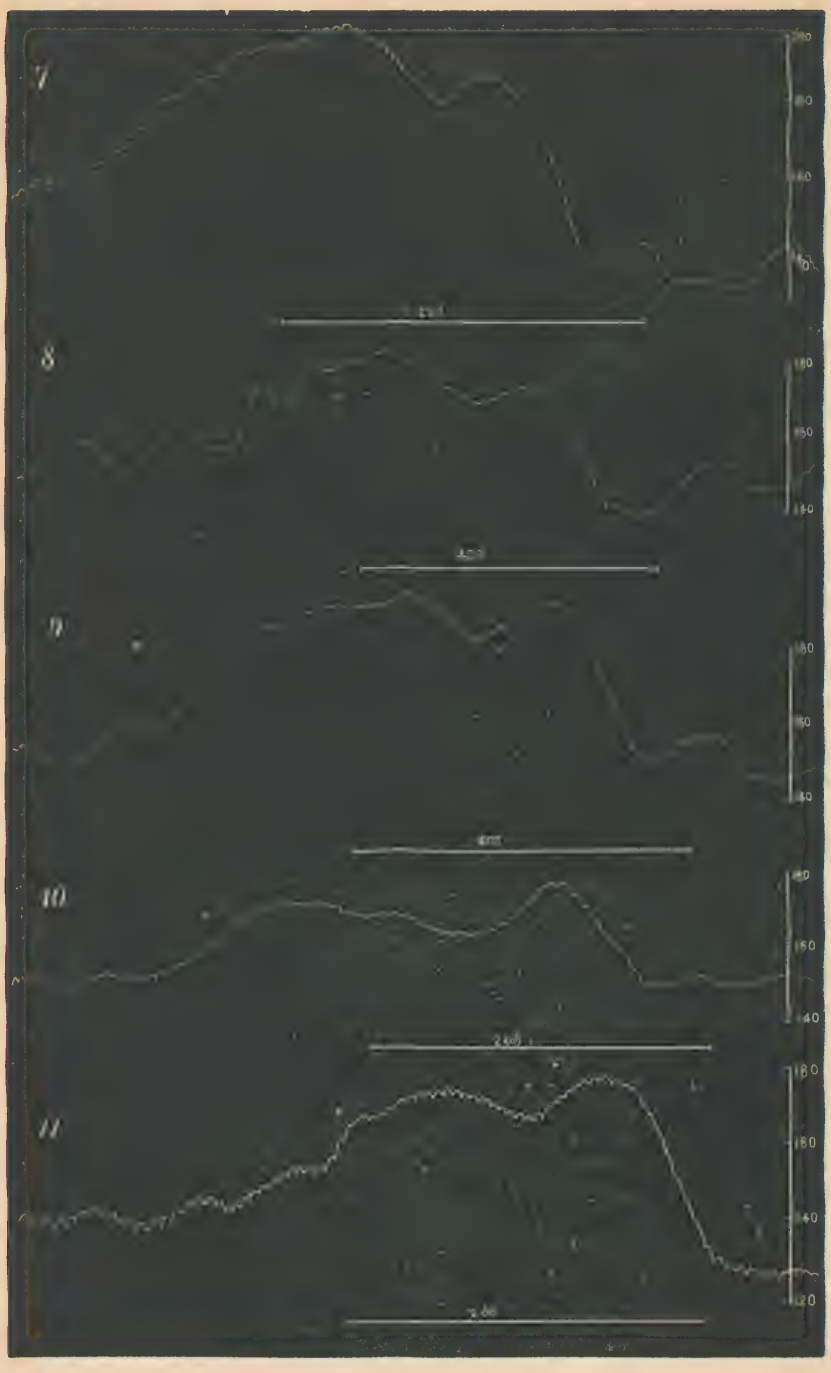
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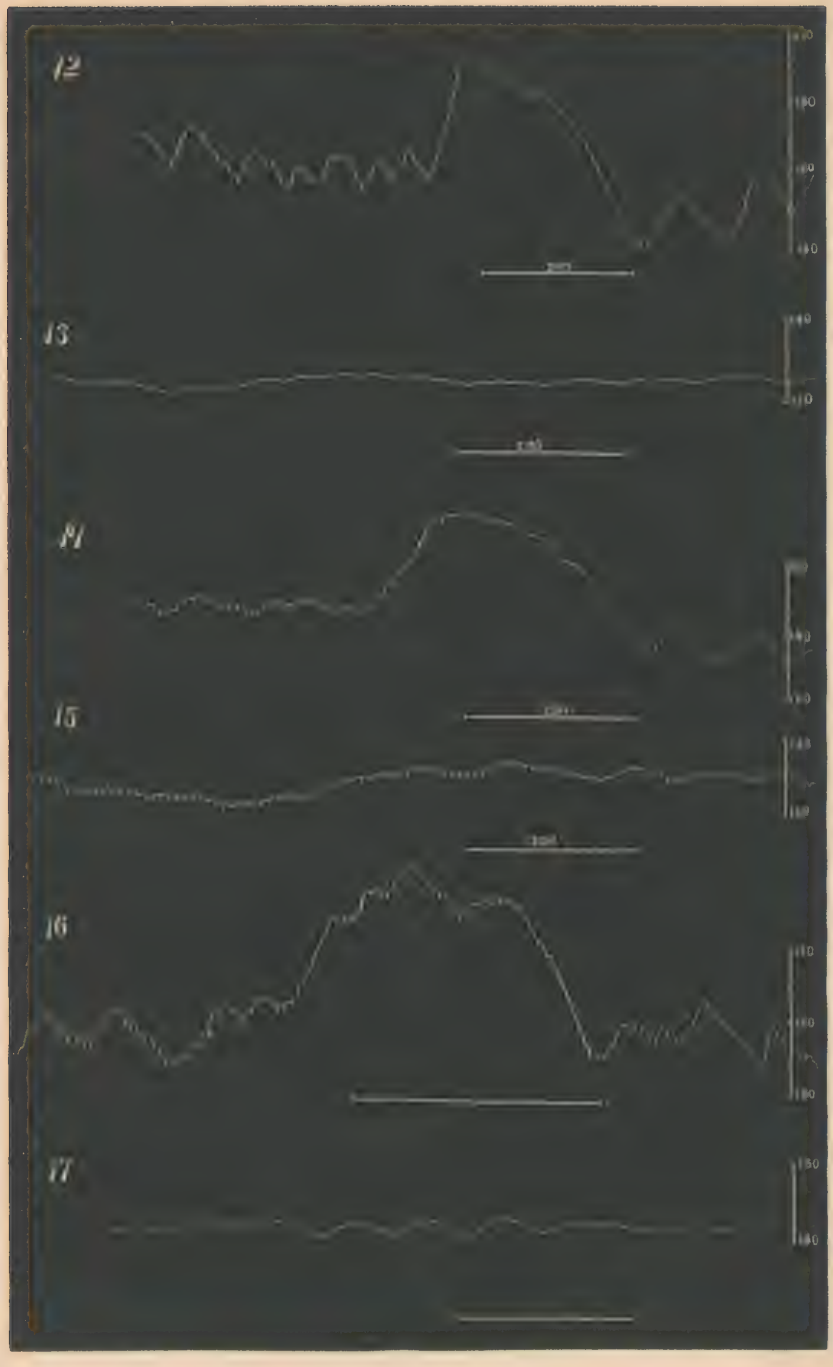
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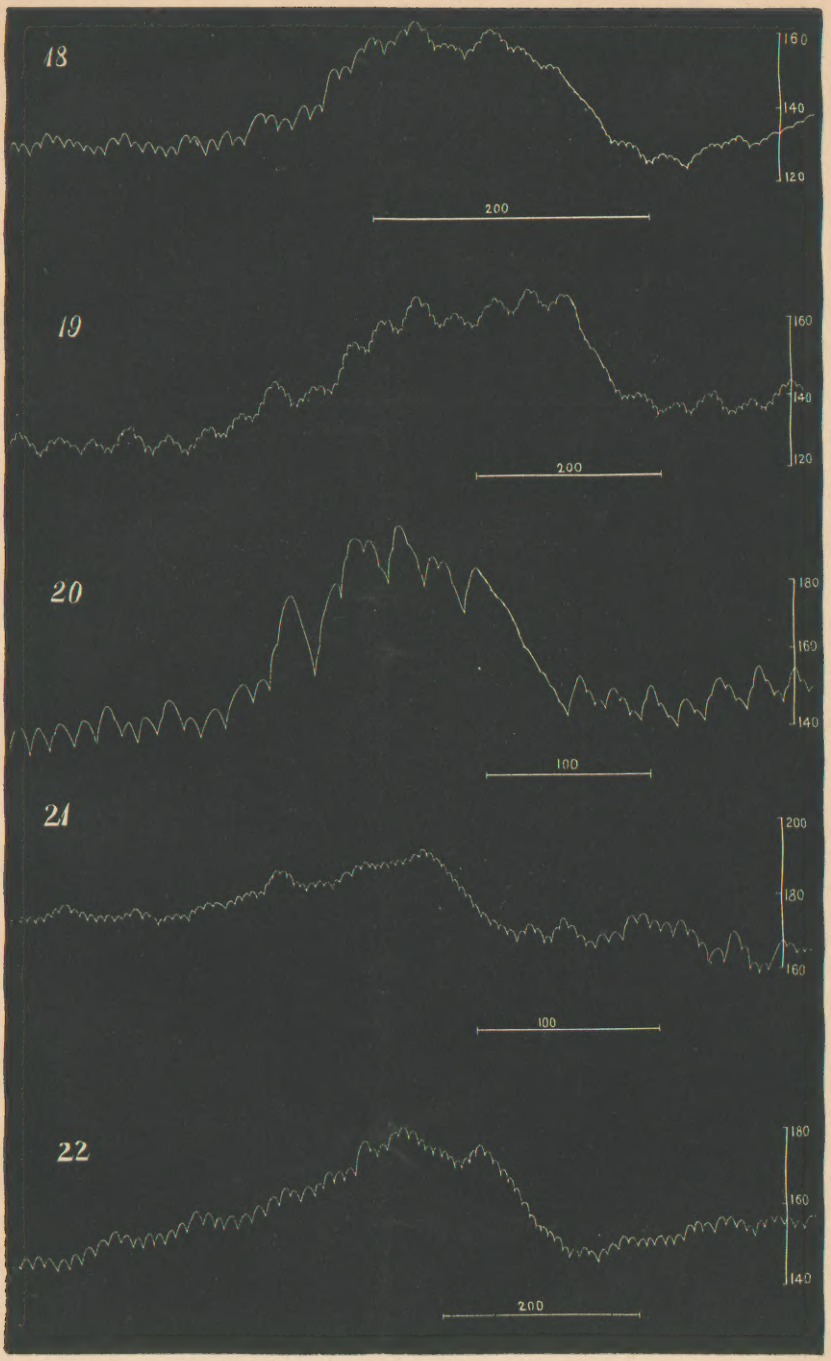
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